REMARKS

The foregoing amendments and the following remarks are submitted in response to the communication dated March 31, 2005.

Status of the Claims

Claims 124, 132-137, 139-143, 145-153, 155-159 and 163-173 are now pending in the application. Claim 160 has been cancelled without prejudice. Claims 124, 132-135, 139-143, 145-150, 152, 155-159 and 163-173 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' Specification.

Specification and Sequence Listing

The examiner has objected to the Specification as failing to comply with the sequence requirements set out in 37 C.F.R. 1.821 through 1.825. In particular, the Examiner asserts that the Sequences on page 158, line 5 and in claims 167 and 168 (gly-ser-pro) do not have a SEQ ID NO. Applicants have above amended the Specification to include SEQ ID NO: references in the text at page 158. This text refers to human met OB DNA and amino acid sequences, which are provided in the Application's Sequence Listing as SEQ ID NOS: 96 and 96, respectively. In addition, Applicants have amended page 1, lines 8-11 and 12, line 2 to update the status of the referenced and priority Applications. The gly-ser-pro sequence now corresponds to SEQ ID NO:100 in the enclosed Sequence Listing. Applicants submit herewith a revised Sequence Listing, as a paper copy and in computer readable form, and Applicants hereby request that the enclosed Sequence Listing be accepted and replace the prior Sequence Listing in the Application. The enclosed Sequence Listing contains no new matter, all sequences having been described and contained in the Specification, including Figures, as filed.

Claim Rejections – 35 USC § 112

Enablement

Claims 124, 132-137, 139-143, 145-149, 155-160 and 163-173 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner sets out rejections as to the breadth of the claims, state of the art regarding the ob gene/protein, unpredictability of gene therapy and teachings of the Specification. Applicants respectfully disagree and assert that the Specification does enable the skilled artisan to make and/or use the invention, and in fact, there have been numerous reports since the time of filing, including the evidence earlier submitted by Applicants in the prosecution of this Application, demonstrating the administration of OB encoding vectors, the expression of OB polypeptide from these vectors, and correction or alteration of body weight *in vivo*. Fletcher et al. (1996) and Muzzin et al. (1996) present studies demonstrating the efficacy of *OB* gene therapy *in vivo* in *ob/ob* mice. Fletcher et al., (1996) also demonstrated the efficacy of *OB* gene therapy in wild-type mice. Each of these references used a different vector to achieve the therapeutic effect. Morsy (1998) demonstrates weight loss following administration of leptin encoded adenoviral vector; that eventual loss of vector occurs does not diminish the evidence it sets out -- that administration, expression and body weight modulation could be achieved by the skilled artisan without undue experimentation.

Without question, there are a variety of viral vectors, of various origin and specificity, to choose from in undertaking gene therapy for expression of any therapeutic polypeptide. The selection and testing of these vectors is undertaken and can be accomplished by the skilled artisan. In addition, the skilled artisan will recognize that expressing a gene in arterial walls for treating restenosis is distinct from OB gene therapy and would not expect the results of Feldman (1995), for instance, to necessarily be relevant to OB therapy, where expression in arterial walls is not particularly targeted.

Contrary to the Examiner's assertion that the instant application does not provide enablement for the claims, Applicants maintain that the specification is a roadmap for how one of skill in the art would modify the body weight of a mammal by administering to the mammal a

vector comprising a nucleic acid molecule encoding an OB polypeptide that is capable of modulating body weight under conditions that provide for expression of the OB polypeptide *in vivo*. To this end, the present application discloses vectors and compositions for use in gene therapy applications. For example, the Specification at page 83 through 85 specifically discusses that gene therapy into human cells would be expected to modulate (decrease or increase) body weight. This section provides exemplary methods of introducing the *OB* gene *in vivo* using, for example, various viral vectors including adenoviruses, retroviruses, adeno associated viruses as well as others. Such vectors were well known to those of skill in the art in 1994, and given the teaching of the present application, one of skill in the art would have been able to employ such vectors in the gene therapeutic applications of the present invention without undue experimentation. In addition to the gene sequences of wild type mouse and human *OB* gene, the present application further describes additional variants and analogs of these genes for use in gene therapy applications.

Applicants disagree with the Examiner's assertion and position that a particular and specific combination of vector (retrovirus,adenovirus, etc.), specific type of administration (tail vein injection), and dosage is essential to the invention. These quantities and types will certainly vary from instance to instance and, Applicants again assert, the determination of these particular parameters are well within the skill of the artisan and do not constitute undue experimentation. It is not necessary or appropriate for the Applicants instant Specification to teach and describe any and all such particular and specific combinations – it is within the skill of the artisan to test and determine them.

In previous responses, Applicants have provided specific examples of areas in which gene therapy has been shown to be successful. Thus, while there may be obstacles in gene therapy methods, such obstacles are not insurmountable and are navigable by those of skill in the art given that the instant application provides details of the gene sequences and vectors that can be used in such protocols in modulating body weight *in vivo*.

Lastly, the Examiner takes the position that the Specification does not enable using a vector encoding an OB protein having substitutions as encompassed by claims 134, 135, 142, 143, 148, 149, 158, 159 and 165-173. The Examiner asserts that the Specification does not define what is considered "conservative" and "non-conservative". Applicants disagree. These claims refer particularly OB polypeptides wherein another amino acid is substituted at any

particular and specified site(s) where the amino acids present in the disclosed mouse and human OB polypeptides are different. A comparison of the mouse and human amino acid sequences aligned with one another, as depicted in the Specification in Figure 4, will readily demonstrate to the skilled artisan those specific amino acids which are different between the human and mouse sequences. It is believed to be particularly straightforward for the skilled artisan to make such a comparison since the length of the mouse and human OB polypeptides are the same and the corresponding amino acids to compare in assessing differences is very readily determined - no gaps exist and no accounting for regions of extra amino acids is necessary. The Specification anticipates variants of OB polypeptides wherein conserved amino acids are substituted ("conserved variants") including at page 5, line 23, at page 8, lines 10 and 20, and at pages 12-13. The term conserved amino acid is well recognized and readily understood by the skilled artisan and refers to the membership of an amino acid in a group defined by one or more particular physical and/or chemical characteristic(s) common to all members of the group. For instance, K (Lysine) and R (Arginine) are both basic and are both positively charged at pH 6.0. Other well recognized groups of conserved amino acids are: (a) S (Serine) and T (Threonine); and (b) V (Valine), I (Isoleucine), L (Leucine) or M (Methionine). Methods for generating any such variant OB polypeptide, using for instance site-directed mutagenesis, were well known in the art even as of the date of filing of the priority application (8-17-94).

New Matter

Claims 124, 132-137, 139-143, 145-149, 155-160 and 163-173 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that a series of phrases and language in the claims is new matter.

The Examiner asserts that the phrase "conditions that provide for expression of the OB polypeptide *in vivo*" and similar phrases in claims 124, 132-135, 139-143, 155-159 and 163-173 is new matter. The Examiner argues that the Specification does not describe any dosage or route of administration for the vectors, which is encompassed by this phrase. Applicants respectfully disagree and assert that the skilled artisan can readily test and identify conditions, including an appropriate vector(s) and expression control sequence(s) for expression of OB polypeptide in an *in vivo* system. In addition the Specification provides teaching and describes and details the

administration of OB polypeptide *in vivo*, including daily administration studies (Example 12), continuous infusion studies (Example 13), dose response studies (Example 15), and assessment of effects on body composition *in vivo* (Examples 16 and 17). Further, Applicants have above amended certain of these rejected claims to modify or eliminate the rejected language, so as to address clarity and definiteness of the claims, therefore the rejection of certain of these claims, including claims 155-159, is now moot.

The phrase "operatively associated with an expression control sequence" in claims 139-143, 145-149 and 155-157 is new matter. Applicants disagree and submit that, in fact, the Specification provides clear support for this phrase. At pages 50-58, the Specification details "production of OB polypeptide: Expression and Synthesis", and at page 51, lines 8-16, sets out and defines operatively linked to an expression sequences, providing evident support for the rejected phrase. The term operatively associated with an expression control sequence is not new matter.

The Examiner rejects "83 percent or more amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOs: 2, 4, 5, 6, 23 or 25" in claims 133 and 147 as new matter. Applicants again disagree and point out that the Specification, including at page 12 line 26 through page 13 line 2, provides specific support and recitation of 83% identity at the amino acid level.

The Examiner asserts that the concept of an OB protein comprising "amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids ... 56 ... [and] ... 95 ... is substituted with another amino acid'' in claims 134, 142, 148 and 158 is new matter. In addition, the concept of an OB protein comprising "amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70 ... 162 and 165 is substituted with another amino acid" in claims 135, 143, 149 and 159 is rejected as new matter. Applicants respectfully disagree and submit that the Specification has clear support for this claim language and for the substitution of these particular amino acids with another amino acid. These rejected claims refer particularly to OB polypeptides wherein another amino acid is substituted at any particular and specified site(s) where the amino acids present in the disclosed mouse and human OB polypeptides are different. A comparison of the mouse and human amino acid sequences aligned with one another, as depicted in the Specification in Figure 4, will readily demonstrate to the skilled artisan those

specific amino acids which are different between the human and mouse sequences. It is believed to be particularly straightforward for the skilled artisan to make such a comparison since the length of the mouse and human OB polypeptides are the same and the corresponding amino acids to compare in assessing differences is very readily determined - no gaps exist and no accounting for regions of extra amino acids is necessary. The Specification anticipates variants of OB polypeptides wherein amino acids are substituted. Claims 134-135, 142-143, 148-149 and 158-159 refer to variant OB polypeptides wherein the particular amino acid present in the disclosed mouse or human OB polypeptide is substituted at any particular and specified site(s) where the amino acids present in the disclosed mouse and human OB polypeptides are different – clearly evident from and described in the Specification and not new matter.

The Examiner further rejects the concept of administering viral vectors by infection or liposome mediated transfection in claim 151 as new matter. Applicants disagree and point to the Specification at page 84, lines 1-16, for description and support for this concept.

The concept of using the early or late SV40, CMV, vaccinia, polyoma, adenovirus, 3-phsphoglycerate kinase or other glycolytic enzyme promoters for gene delivery in a mammal as in claim 160 is rejected as not having support in the specification as originally filed. Applicants again submit that the Specification supports this concept. In particular, page 52 line 25 through page 53 line 8 provides specific textual support for the use of early or late SV40, CMV, vaccinia, polyoma, adenovirus, 3-phsphoglycerate kinase or other glycolytic enzyme promoters in controlling gene expression.

Lastly, the Examiner asserts that claims 165-173 are new matter, stating that: the specific substitutions in claims 165, 166, 170, 171 and 173; the N-terminal amino acids in claims 167 and 168; and the "truncated analogs" in claims 169 and 172 cannot be found in the Specification. The Specification discusses and provides support for the various amino acid substitutions, amino acid deletions (truncated analogs) set out in claims 165, 166, 169, 170, 171, 172 and 173, including at page 32 line 15 through page 35 line 11. These portion of the Specification sets out each of the substitutions and truncated analogs claimed. The N-terminal amino acids set out in claims 167, 168, and 173, and recited in subparts h) of claims 169 and 172 are supported in the Specification, including in Figures 21 and 22, in the Figure legends at page 18 and in Example 6, which details expression and various constructs in yeast and using His tags. Each of these N

terminal amino acid sequences are depicted and described and they therefore do not constitute new matter as set out in the claims.

Indefiniteness

The Examiner has rejected claims 124, 132-137, 139-143, 145-149, 155-160 and 163-173 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

Claims 124, 132-137 and 165-173 are rejected as indefinite because the body of the claim does not recite a clear positive step in which the body weight of the mammal is modified. Applicants have above amended these rejected claims to recite a clear positive step commensurate with the claim language, as to body weight modification, expression, etc., and assert that these amendments address this rejection.

Claims 139-142 are indefinite because the body of the claim does not recite a clear positive step of delivering. Applicants have above amended claims 139-143 to include a delivering step.

Claims 144-149 and 155-159 are indefinite because the body of the claim does not recite a clear positive step of expressing an OB polypeptide. Applicants point out that claim 144 is a canceled claim. Applicants have above amended claims 145-149 and 155-159 to incorporate language whereby said OB polypeptide or polypeptide analog is expressed.

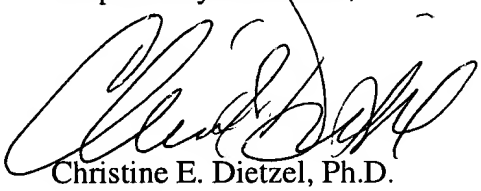
Finally, the Examiner rejects the phrase "such OB encoding DNA" in claim 140 as lacking antecedent basis. Applicants respectively disagree and point out that the antecedent phrase 'DNA encoding an OB polypeptide' is present in the preamble language of claim 140, giving basis for the reference phrase.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's enablement, new matter and indefiniteness rejections under 35 USC 112, second paragraph, should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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